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2-(3-*tert*-Butyldimethylsiloxy-4-methoxyphenyl)-6-methoxy-3-(3,4,5-trimethoxybenzoyl)indole

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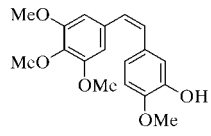
In the crystal structure of the title compound, $C_{32}H_{39}NO_7Si$, all geometric parameters fall within experimental error of expected values. The analysis of molecular-packing plots reveals an infinite two-dimensional linear array running parallel to the *b* axis, formed by one N—H···O intermolecular hydrogen-bonding interaction. Several potential C—H···O interactions are also present.

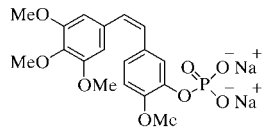
Comment

The protein tubulin plays a vital role during mitosis through polymerization and depolymerization. Inhibitors of tubulin polymerization are known to arrest the assembly of tubulin into microtubules, resulting in the disruption of cell division (Hamel, 1996). Recently, it has been established that some of these agents rapidly shut down tumor vasculature, which results in necrosis of the tumor cells (Galbraith *et al.*, 2001; Tozer *et al.*, 1999). Combretastatin A-4 (CA-4), (I) (Pettit *et al.*, 1982, 1987, 2000), interacts with the colchicine binding site with a high binding affinity and inhibits the assembly of tubulin into microtubules (Hamel & Lin, 1983), while its corresponding water-soluble prodrug, disodium phosphate CA-4P, (II) (Pettit & Rhodes, 1998), is inactive with tubulin. It is suggested that the phosphate moiety navigates the molecule in selectively targeting the sites of increased vascularization, as it undergoes dephosphorylation at these sites by the action of endothelial alkaline phosphatases, which release the active form of the drug, CA-4.

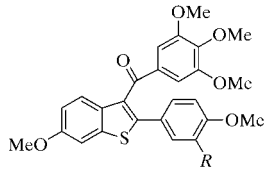
Two benzo[*b*]thiophene analogs, *i.e.* (III) and (IV), which bear structural features similar to CA-4, demonstrate excellent cytotoxicity and inhibition of tubulin polymerization (Mullica *et al.*, 1998; Pinney *et al.*, 1998, 1999; Flynn *et al.*, 2001). Encouraged by these promising research results, we synthesized an indole variant as both the free phenol, (V), (Pinney *et al.*, 2001; Flynn, 2001; during the preparation of this manuscript, we learned that this compound had also been prepared independently by an alternate synthetic route), and its corresponding *tert*-butyldimethylsilyl ether, (VI), which will eventually be converted to its water-soluble phosphate prodrug form.



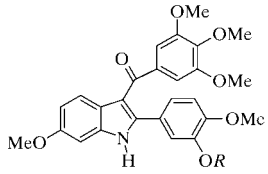
(I)



(II)



(III) R=H
(IV) R=OH



(V) R=H
(VI) R=Si(^{t}Bu)Me$_2$

In order to unequivocally confirm the molecular structure, as well as gather information paramount for our molecular recognition studies, we have determined the crystal structure of (VI).

Fig. 1 shows the molecular structure of (VI), while selected geometric parameters are presented in Table 1. All internuclear distances and angles fall within the range of expected values and are comparable with those found in the related benzo[*b*]thiophene (III) structure determined by Mullica *et al.* (1998).

The indole ring is planar within 0.028 Å and forms respective dihedral angles of 49.50 (9) and 46.97 (7)° with the methoxyphenyl and trimethoxybenzoyl moieties. The latter two ring systems are also planar, within 0.005 and 0.009 Å, respectively, and exhibit a dihedral angle of 48.93 (10)°, with a centroid-to-centroid separation of 4.36 Å.

The methoxy substituents on the several ring systems are rotated by various intervals to accommodate steric and crystal-packing requirements. Appropriate torsion angles are

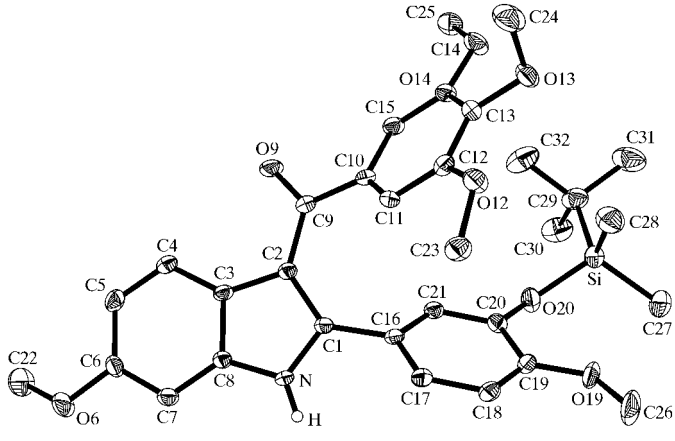


Figure 1
Displacement ellipsoid plot (40% probability) of (VI) with the atom labels. All H atoms, except for the indole NH atom, have been omitted for clarity.

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given in Table 1. Most notably, the methoxy group in position 4 of the 3,4,5-trimethoxybenzoyl component is rotated approximately 92.5° from the least-squares plane of the ring, with the terminal C24 atom extending 1.332 Å from the ring. The remaining substituents on the same group are twisted by 13.3 and 3.8°, respectively, with C23 and C25 protruding by 0.275 and 0.040 Å, respectively, above and below the ring. Elsewhere, the methoxy groups on the TBS–methoxyphenyl (TBS is *tert*-butyldimethylsiloxy) and methoxyindole moieties are turned by 12.9 and 25.1° from their respective ring planes; atoms C26 and C22 project from their corresponding rings by 0.207 and 0.632 Å, respectively.

The supramolecular structure of (VI) consists of corrugated ribbons formed by an infinite linear array of molecules linked by an intermolecular N—H···O hydrogen-bonding interaction. According to Etter's graph-set analysis, this hydrogen-bond system is designated $C(6)$ (Etter *et al.*, 1990; Bernstein *et al.*, 1995) and runs parallel to the *b* axis of the crystal lattice. Additionally, several other O atoms are involved in multiple close contacts with the H atoms of various adjacent groups. According to the somewhat liberal definition ascribed by Desiraju & Steiner (1999), these contacts may be classified as weak C—H···O hydrogen bonds; details are included in Table 2.

Experimental

To a well stirred solution of 2-(3-*tert*-butyldimethylsiloxy-4-methoxyphenyl)-6-methoxyindole (0.511 g, 1.33 mmol) in *o*-dichlorobenzene (10 ml) was added 3,4,5-trimethoxybenzoyl chloride (0.464 g, 2.01 mmol, 1.51 equivalents). The reaction mixture was refluxed for 12 h, after which the excess of *o*-dichlorobenzene was removed *in vacuo* and the resulting dark solid was subjected to flash chromatography (silica gel, 25% EtOAc in hexanes) to afford the title compound as a yellow powder. Recrystallization from hexanes–EtOAc afforded indole (VI) as prismatic pale-yellow crystals (0.355 g, 0.614 mmol, 46% yield, m.p. 438–440 K). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.035 (3H, *s*), 0.93 (9H, *s*), 3.69 (6H, *s*), 3.75 (3H, *s*), 3.79 (3H, *s*), 3.87 (3H, *s*), 6.71 (1H, *d*, J = 8.8 Hz), 6.77 (1H, *d*, J = 2.3 Hz), 6.87–6.94 (3H, *m*), 6.99 (2H, *s*), 7.95 (1H, *d*, J = 9.9 Hz), 8.39 (1H, *s*, broad).

Crystal data

$C_{32}H_{39}NO_7Si$
M_r = 577.73
Orthorhombic, *Pbca*
a = 14.596 (1) Å
b = 14.753 (1) Å
c = 28.531 (4) Å
V = 6143.8 (10) Å^3
Z = 8
D_x = 1.249 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 10.1–16.2°
μ = 0.12 mm^{-1}
T = 173 (2) K
Prism, pale yellow
0.55 × 0.49 × 0.49 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: ψ scan (*SHELXTL*/*PC*; Sheldrick, 1995)
T_{min} = 0.926, T_{max} = 0.945
5570 measured reflections
5335 independent reflections
3841 reflections with $I > 2\sigma(I)$
R_{int} = 0.017
θ_{max} = 25.0°
$h = 0 \rightarrow 17$
$k = 0 \rightarrow 17$
$l = -2 \rightarrow 33$
3 standard reflections
frequency: 120 min
intensity decay: 10.1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.048
$wR(F^2)$ = 0.127
S = 1.08
5335 reflections
374 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0242P)^2 + 12.4107P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.37 e Å^{-3}
$\Delta\rho_{min}$ = −0.41 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.00155 (13)

Table 1
Selected geometric parameters (Å, °).

N—C1	1.364 (4)	C20—O20	1.368 (4)
N—C8	1.384 (4)	C22—O6	1.429 (4)
C6—O6	1.376 (3)	C23—O12	1.430 (3)
C9—O9	1.233 (3)	C24—O13	1.430 (4)
C12—O12	1.362 (3)	C25—O14	1.429 (4)
C13—O13	1.378 (3)	C26—O19	1.427 (4)
C14—O14	1.360 (3)	O20—Si	1.673 (2)
C19—O19	1.362 (3)		
C1—N—C8	110.2 (2)	O20—C20—C21	119.3 (3)
N—C1—C16	117.9 (2)	O20—C20—C19	120.5 (3)
O6—C6—C7	115.5 (3)	C6—O6—C22	117.4 (2)
O6—C6—C5	123.6 (3)	C12—O12—C23	117.0 (2)
O9—C9—C2	119.5 (3)	C13—O13—C24	112.5 (2)
O9—C9—C10	118.5 (3)	C14—O14—C25	117.7 (2)
O12—C12—C11	125.1 (3)	C19—O19—C26	117.2 (3)
O12—C12—C13	114.9 (3)	C20—O20—Si	128.80 (19)
O13—C13—C12	119.9 (3)	O20—Si—C28	110.01 (15)
O13—C13—C14	119.7 (3)	O20—Si—C27	109.48 (15)
O14—C14—C15	125.4 (3)	C28—Si—C27	112.12 (18)
O14—C14—C13	115.2 (3)	O20—Si—C29	103.55 (14)
O19—C19—C18	125.5 (3)	C28—Si—C29	111.06 (17)
O19—C19—C20	115.0 (3)	C27—Si—C29	110.29 (17)
C16—C1—C2—C9	−9.8 (6)	C11—C12—O12—C23	14.1 (4)
C1—C2—C9—C10	−21.8 (5)	C13—C12—O12—C23	−167.5 (3)
C3—C2—C9—C10	158.3 (3)	C12—C13—O13—C24	−88.5 (3)
O12—C12—C13—O13	1.7 (4)	C14—C13—O13—C24	93.5 (3)
O13—C13—C14—O14	−0.3 (4)	C15—C14—O14—C25	3.4 (4)
N—C1—C16—C17	−49.2 (4)	C13—C14—O14—C25	−175.8 (3)
N—C1—C16—C21	128.1 (3)	C18—C19—O19—C26	−13.6 (4)
O19—C19—C20—O20	0.7 (4)	C20—C19—O19—C26	167.8 (3)
C7—C6—O6—C22	−155.2 (3)	C21—C20—O20—Si	124.8 (3)
C5—C6—O6—C22	25.4 (5)	C19—C20—O20—Si	−57.9 (4)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N—H···O9^{i}	0.83 (3)	2.10 (3)	2.922 (4)	170 (3)
C4—H4···O9	0.95	2.52	3.022 (4)	113
C22—H22*A*···O12^{ii}	0.98	2.53	3.224 (4)	127
C26—H26*C*···O13^{iii}	0.98	2.53	3.171 (4)	123
C27—H27*A*···O19	0.98	2.58	3.194 (4)	121

Symmetry codes: (i) $-\frac{1}{2}-x, \frac{1}{2}+y, z$; (ii) $x-1, y, z$; (iii) $\frac{1}{2}-x, \frac{1}{2}+y, z$.

The indole H(—N) atom was located in a difference Fourier synthesis and was allowed to refine with a fixed isotropic displacement parameter of U_{iso}(H) = 1.2U_{eq}(N). All other H atoms were constrained to idealized geometries (C—H = 0.95 or 0.98 Å) and were assigned isotropic displacement parameters of U_{iso}(H) = 1.2U_{eq}(C), or U_{iso}(H) = 1.5U_{eq}(C) for methyl H atoms. The final electron-density difference synthesis indicated a randomly fluctuating background with no significant residual peaks.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *XCAD*4 (Harms, 1993); program(s) used to solve structure: *SHELXTL*/*PC* (Sheldrick, 1995); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XP* in *SHELXTL*/*PC*; software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: BK1630). Services for accessing these data are described at the back of the journal.

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